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CHRONIC FATIGUE SYNDROME PATHOPHYSIOLOGY

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National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Mental Health
National Heart, Lung, and Blood Institute
National Institute of Environmental Health Sciences
National Institute of Nursing Research
National Institute of Diabetes and Digestive and Kidney Diseases
Office for Research on Women's Health

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Mental Health (NIMH), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Environmental Health Sciences (NIEHS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Nursing Research (NINR), and the Office for Research on Women's Health (ORWH) invite submission of investigator-initiated research grant applications to support research on the pathophysiology of chronic fatigue syndrome (CFS). Applications are encouraged that address new hypotheses and research gap areas or that are small studies that explore new ideas.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This program announcement, Chronic Fatigue Syndrome Pathophysiology, is related to the priority area of chronic disabling diseases. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-0325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators. Foreign institutions are not eligible for the First Independent Research Support and Transition (FIRST) award (R29).

MECHANISM OF SUPPORT

Traditional research project grant (R01) and FIRST award (R29) applications may be submitted in response to this program announcement. The R01 mechanism can be used to support small studies. Funds and time requested should be appropriate for the research proposed. Several Institutes use specialized mechanisms such as the small research grant (R03); if you believe that your project is appropriate for such a mechanism, consult the individuals listed in the INQUIRIES section.

RESEARCH OBJECTIVES

Background

Chronic fatigue syndrome (CFS) is a multisystem syndrome characterized by months of debilitating fatigue frequently associated with myalgia, headache, sore throat, low grade fever, cognitive complaints, gastrointestinal symptoms, and tender lymph nodes. The cause(s) and pathogenic mechanism(s) of the illness remain unknown. The range of symptoms and comparisons of CFS patients with healthy persons and with other chronically ill persons suggest subtle perturbations in multiple physiological pathways. However, no single marker or

physiological alteration has been identified that can be used to diagnose the syndrome. CFS is diagnosed three to four times more frequently in women than in men and about 10 times more often in white Americans than in other American population groups.

Research Objectives and Experimental Approaches

Well-designed studies are needed to provide a better understanding of CFS pathogenesis with the goal of developing diagnostic and intervention strategies. Studies should include appropriate sample sizes and test biologically rational hypotheses. Selection criteria and procedures for CFS cases and comparison groups should be carefully delineated and appropriate for the hypothesis under study. Factors which may explain or have an impact on CFS pathogenesis and areas needing additional research include, but are not limited to:

o low levels of cortisol and corticotropin-releasing hormone in CFS patients in the absence of documented adrenal-hypothalamic axis dysfunction attributable to other causes

o overlapping symptomatology with neurally-mediated hypotension

o role of cardiovascular regulatory centers in the brain stem, hypothalamus, and higher cortical regions in the loss of the normal control of blood pressure, heart rate, and contractility in CFS patients.

o dysfunctions in the baroreceptor, ventricular mechanoreceptor, and other cardiovascular reflex pathways in the chronic fatigue syndrome and in acute and chronic episodes of hypotension and syncope observed in CFS patients.

o development of novel cardiovascular pharmacological and non-pharmacological interventions for treatment of CFS patients.

o development of novel and objective cardiovascular markers for the diagnosis of CFS.

o interaction of cytokines with physiological systems other than the immune system as effectors of CFS pathogenesis

o increased frequency of sleep disturbances (hypersomnia or insomnia)

o overlapping symptomatology with fibromyalgia

o role of neuroendocrine and neuroimmune functions in CFS pathogenesis

o hormonal effects, including in pregnancy, on illness severity and/or symptomatic improvement

o low tolerance to physical exertion manifested by prolonged generalized fatigue after very moderate exercise

o potential role of viruses or other infectious agents as markers of disease pathogenesis or as co-factors in pathophysiological processes.

o lymphocyte patterns suggestive of immune activation (e.g., alterations in T-cell subsets number and function, altered cytokine levels and function)

o increased frequency of psychiatric diagnoses in CFS patients (except those that would exclude an individual from the CFS case definition)

o increased frequency of atopy in CFS patients compared with the U.S. population as a whole

o role of environmental agents as etiological or pathophysiological factors

o gender specific factors in etiology and disease progression

o highly active lifestyle prior to onset of CFS

o epidemiology, natural history and pathophysiology of CFS in less studied populations such as children, adolescents, minorities, men

o demographic risk factors (gender, age, race, socioeconomic class)

Applications for small studies that explore new ideas are also encouraged and could provide the basis for submission of a subsequent larger grant application.

Study Design and Methodological Issues

Multidisciplinary studies and collaboration among investigators with expertise in appropriate disciplines are encouraged. When investigators are at different institutions, individual R01 applications may include consortium arrangements.

Collaborative arrangements with on-going studies that provide patient populations, specimens and data are encouraged. Such arrangements should be clearly delineated in the application.

The methodologies and personnel involved in statistical/epidemiological analyses should be described in the application and evident in the study design. The hypothesis(es) to be tested should be clearly stated. The constructs and measurements to be used operationally to obtain statistically and biologically meaningful results should be clearly defined and enumerated.

The value of studies of patients or their specimens will be directly related to the care exercised in selection and initial characterization of cases and controls. A detailed description of case recruitment procedures, the criteria to be used for case definition and the manner in which the criteria are to be applied must be included. Similar care should be given to descriptions of enrollment of comparison groups. Investigators are encouraged to use the CFS case definition as presented in Fukuda, et. al., Annals of Internal Medicine: 121, 953-9, 1994. If other case definitions are proposed, they should be clearly defined and the rationale for their choice clearly delineated.

Applications to estimate the frequency of physiological or behavioral variables or responses, or to address other quantitative aspects in relevant populations should pay particular attention to sample sizes required to attain the degree of precision sought or needed for statistically and biologically meaningful results. The reliability and validity of markers chosen for measurement should be demonstrated. Applications attempting to examine interrelationships among two or more separate factors are encouraged to the extent that the types and numbers of subjects are sufficient for such comparisons.

The measurement of many markers, including immunological, virological, physiological and psychological markers, are dependent on the measurement system chosen and its execution. Thus, it is very important that applicants clearly define the methodologies to be used, the rationale for choosing that methodology and for validating results as well as methods of collection, processing, and storage of samples and data. When conflicting results have been reported in the literature, applicants should provide possible explanations for such variability and indicate how their approach might resolve the issue.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations) which have been in effect since 1990. The new policy contains some new provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research", which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513), and reprinted in the NIH GUIDE FOR GRANTS AND CONTRACTS of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies from these sources or from the program staff or contact persons listed below. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 5/95) and will be accepted on the standard application deadlines as indicated in the application kit. Applications kits are available at most institutional offices of sponsored research and may be obtained from the Grants Information Office, Office of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: ASKNIH@odrockm1.od.nih.gov.

Each application must be identified by checking "YES" on line 2 of the PHS face page, and the number and title of this program announcement must be typed in section 2.

The completed original and five legible, single-sided copies of the application must be sent or delivered to:

DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for courier/overnight service)

FIRST (R29) award applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST (R29) award applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be reviewed for scientific and technical merit by study sections of the Division of Research Grants, NIH, in accordance with the standard NIH peer review procedures. Following scientific/technical review, the applications will receive secondary review by the appropriate national advisory council.

Review Criteria

o scientific, technical, or medical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

o availability of the resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research;

o adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

The initial review group will also examine the provisions for the protection of human and animal subjects and the safety of the research environment.

AWARD CRITERIA

Applications will compete for available funds with all other favorably recommended applications assigned to an Institute or Center. The following will be considered when making funding decisions: quality of the proposed project as determined by peer review, program balance among research areas of the announcement, and availability of funds.

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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Direct inquiries regarding fiscal matters to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.856, Microbiology and Infectious Disease Research; No. 93.846, Arthritis, Musculoskeletal, and Skin Diseases Research; No.93.837, Heart and Vascular Diseases Research; No. 93.361, Nursing Research; No. 93.242, Mental Health Research; No. 93.847 Diabetes, Endocrinology, and Metabolic Diseases Research; and Nos. 93.113, 93.115 Environmental Health Research. Awards are made under authorization of the Public Health Service Act, Title IV, Part A

(Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The Public Health Service (PHS) strongly encourages all grant and contract recipients to provide a smoke-free work place and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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